(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/67946 A1

(51) International Patent Classification[7]: A61B 5/00

(21) International Application Number: PCT/IL01/00250

(22) International Filing Date: 15 March 2001 (15.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
135077 15 March 2000 (15.03.2000) IL

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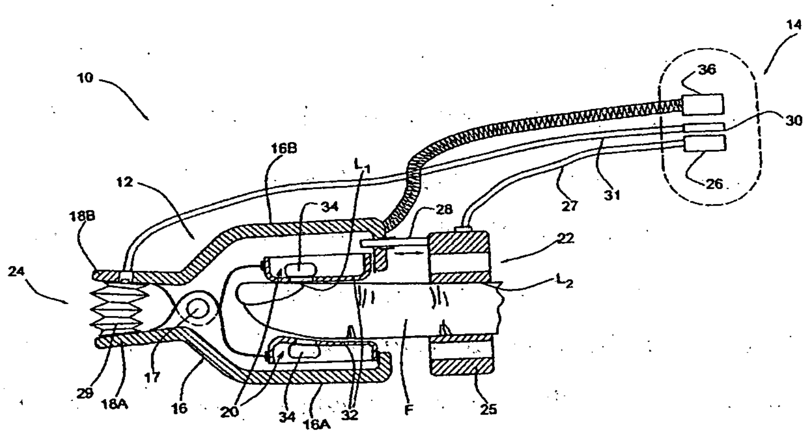
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A PROBE FOR USE IN NON-INVASIVE MEASUREMENTS OF BLOOD RELATED PARAMETERS



(57) Abstract: A probe device for use in non-invasive optical measurements of at least one parameter of the patient's blood. The probe device comprises a finger holder in the form of a clip member (16) that secures a fingertip between its clamping legs (16A, 16B). The probe device supports a measuring unit (20) for applying optical measurements to a measurement location on the finger, and carries a pressurizing assembly (24) operable for applying controllably variable, substantially under-systolic pressure to the finger in the vicinity of the measurement location. Several measurement sessions are performed at the measurement location with at least two different wavelength of incident light to detect light response of the medium and generate measured data indicative thereof, and the pressure applied to the vicinity of the measurement location is simultaneously varied during measurements. The light response of the medium corresponding to different wavelength of the incident light and different pressure values is analyzed, and an optimal pressure value is determined, so as to utilize the corresponding light response of the medium for deriving therefrom the at least one blood parameter.

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A Probe for Use in Non-Invasive Measurements of Blood Related Parameters

FIELD OF THE INVENTION

This invention is generally in the field of non-invasive optical measurement techniques for measuring blood parameters, and relates to a probe to be applied to a patient's finger.

BACKGROUND OF THE INVENTION

Non-invasive techniques for measuring various blood parameters, such as blood oxygen saturation and the concentration of substances contained in the blood (hemoglobin, glucose and other substances) have become very popular, since they do not require the withdrawal of a blood sample from a patient's body. Optical monitoring techniques of the kind specified typically utilize the detection of light transmitted or reflected from the location on the patient's body under measurement, and are based on spectrophotometric measurements enabling the indication of the presence of various blood constituents based on known spectral behaviors of these constituents. Most of these techniques utilize a measurement optical device or probe, designed in a manner to be attached to the patient's finger, which includes an optical assembly for irradiating the finger with light and detecting its light response.

US Patent No. 5,810,723 discloses an apparatus for the non-invasive monitoring of a patient's carboxyhemoglobin level. The patient breathes oxygen to saturate his blood hemoglobin prior to detection. The apparatus utilizes a clamp with arms holding the patient's finger: one arm supports a light emitting source and the other supports a detector. A microprocessor controls the measurements and processes the detected signals.

US Patent 5,638,816 and its continuation, US Patent 5,860,919, disclose an apparatus for the non-invasive monitoring of blood parameters by applying pressure to the patient's finger, thus inducing an active pulse therein. The induced change of blood volume enables a better signal-to-noise ratio to be obtained.

US 5,782,757 discloses a measuring devices in the form of disposable, folded adhesive sensors with optics embedded therein. The probe is designed so as to fit comfortably onto a patient's fingertip.

All the conventional devices of the kind specified are aimed at measuring enhanced optical pulsatile signals caused by the changes in the volume of the blood containing medium (finger). It is known that a regular optical pulsatile signal is typically 2-3% of the total transmission. The above devices are capable of obtaining the enhanced pulsatile signal that reach 8-10% of the total light transmission intensity. This enhancement of the natural pulsatile signal is a boundary of all conventional techniques of the kind specified.

A different technique is disclosed in a PCT application, International Publication No. WO 99/65384, assigned to the assignee of the present application. This is an occlusion based technique, where the measured signals are not pulsatile. According to this technique, the state of blood cessation is created in a medium under measurement, and measurements are taken during this state. This enables to obtain a significantly enhanced light response of the medium, as compared to that of the previously described techniques dealing with the pulsatile signals. To create such a state of blood cessation, over-systolic pressure needs to be applied to the patient's finger at a location upstream of the area under measurement, with respect to the direction of normal blood flow. Once the blood flow cessation state is

established, the optical characteristics start to change dramatically, such that they differ from those of the fleshy medium with a normal blood flow by about 25 to 45%, and sometimes even by 60 %. At least two timely separated measurement sessions are performed, each including at least two measurements with different wavelengths of incident radiation. None of the conventional probes is suitable for these purposes. A probe in the form of a finger holder, suitable for applying over systolic pressure to a first location on the patient's finger and applying optical measurements to a second location downstream of the first location, is disclosed in a co-pending US application Serial No. 09/407390, assigned to the assignee of the present application.

SUMMARY OF THE INVENTION

There is a need in the art to further improve non-invasive measurements of blood parameters, by providing a novel probe device to be used in non-invasive optical measurements enabling the application of a variable controlled pressure to the patient's organ (e.g., his finger) in the vicinity of a measurement location.

It is a major object of the present invention to provide such a device that optimizes the finger tissue and blood volume, thereby providing conditions for measurements with maximum accuracy.

It was found by the inventors that the accuracy of the measured signal can be improved even more by applying certain under-systolic pressure (0-250mmHg) to a region in the vicinity of a measurement location. This pressure, required for significantly improving the accuracy of measurements, may be different for different patients, depending *inter alia* on the internal blood pressure of the specific patient, and individual peculiarity of the finger size, shape and physiological conditions. This optimal pressure value depends also on the rigidity of the construction of probe device itself. Therefore means should be provided enabling to controllably vary the magnitude of the applied pressure.

Generally speaking, the present invention provides an active sensing means that enables to select an optimal pressure for a specific patient, such that the

application of this pressure provides an optimal optical measurement signal for deriving therefrom the correct value of the parameter to be measured. In other words, the present invention enables to adjust the conditions of a measurement location on the patient's organ to the optimal signal determination.

Thus, according to one broad aspect of the present invention, there is provided a method of non-invasive optical measurement of at least one parameter of the patient's blood, the method comprising the steps of:

(a) applying a probe device to the patient's blood perfused fleshy medium, wherein the probe device carries an optical measurement unit and a pressurizing assembly operable to apply controllably varying substantially under-systolic pressure to a measurement location on said medium;

(b) performing several measurement sessions to a measurement location on said medium to detect light response of the medium and generate measured data indicative thereof, and simultaneously varying the pressure applied to the vicinity of said measurement location, wherein each measurement session utilizes at least two different wavelength of incident light;

(c) analyzing the light response of the medium corresponding to different wavelengths of the incident light and different pressure values, and determining an optimal pressure value, so as to utilize the corresponding light response of the medium for deriving therefrom said at least one blood parameter.

Preferably, the method according to the invention also comprises the application of over-systolic pressure to a location upstream of the measurement location, with respect to the direction of normal blood flow in the medium, so as to create the state of blood flow cessation. In this case, the measurements are taken during this state. Several time-separated measurement sessions can be performed either during the single blood-cessation state, or during the sequential blood cessation state. The latter operational mode is actually the so-called

"multiple-occlusion", obtained by sequentially applying and releasing the over-systolic pressure.

Parameters that can be measured include oxygen saturation and the concentration of substance in blood, such as hemoglobin, glucose, etc. The present invention may utilize a calibration stage, during which various patients undergo measurements, and calibration curves corresponding to different blood parameters as functions of the applied under-systolic pressure are plotted.

The wavelengths of incident light are selected in accordance with the parameter to be measured. Preferably, several different wavelengths are sequentially applied, so as to obtain data from which different blood parameters can be derived within the same measurement session.

The probe device according to the invention utilizes a finger holder carrying a measurement unit and a pressurizing assembly, all operated by a control system. The measurement unit typically comprises illumination and detection systems, arranged so as to detect reflected or transmitted light, as the case may be. The pressurizing assembly is designed so as to apply variable controlled pressure to the tissue in the vicinity of the measurement location.

Generally, the probe device may be associated with any other suitable patient's organ, such as his hand or wrist. If the patient's hand is considered, the rigid connector engages the patient's arm to prevent its folding at the elbow joint. It is more practical, however, to apply the device to the patient's finger.

The finger holder is in the form of a clip securing the fingertip between its legs and carrying the measurement unit. The clip may be formed with one pair or two pairs of legs. The four-leg design advantageously enables to provide four-sided support for the finger, thereby preventing its folding at the distal phalanx. A pair of manipulating arms is used for opening and closing the clip when putting the device in operation. In the case of the two-legged design, the extensions of the legs serve as the manipulating arms. In the case of the four-legged design, the manipulating arms are coupled to the legs through any suitable mechanism, enabling the simultaneous pivotal movement of all the legs.

The pressurizing assembly is of a pneumatic type. According to one embodiment of the invention, the pressurizing assembly comprises a bellow-like cushion, which is interconnected between the manipulating arms by its opposite ends and is coupled to the drive operated by the control system. The expansion and squeezing of the sleeve thus operates the pivotal movement of the manipulating arms, thereby weakening or enhancing the clamping effect of the clip legs. According to another embodiment of the invention, the pressurizing assembly comprises a balloon-like flat cushion attached to the inner side of the clip between its upper leg and a flexible cushion-like member contacting the patient's finger, so as to press on the finger portion below the clip. In this case a locking device is provided to prevent the opening of the clip. According to yet another embodiment of the invention, the pressurizing assembly comprises a ring-like cushion attached to the inner side of the clip so as to wrap the finger, when putting the device into operation. The control system operates the expansion and squeezing of the cushion.

- There is thus provided according to another aspect of the invention, a probe device to be used in non-invasive optical measurements of a patient's blood parameters, the probe device comprising a finger holder having a clip member that secures a fingertip between its clamping legs, wherein the finger holder supports a measuring unit for applying optical measurements to a measurement location on the finger, and carries a pressurizing assembly operable for applying controllably variable, substantially under-systolic pressure to the finger in the vicinity of said measurement location.

The probe device may be used with a pulse oxymeter, wherein the application of the controllably varied under-systolic pressure enables to derive more information from measured signals. This information contains the maximal amplitude of a pulsatile signal and/or AC/DC ratio.

Thus, according to yet another aspect of the present invention, there is provided a pulse-oxymeter utilizing the above probe device and a control system that operates the pressurizing assembly and the measurement unit and generates data indicative of the measured parameters.

Preferably, the probe device also comprises an additional pressurizing assembly, which may also be of a pneumatic type, and operated by the same drive means as the above-described pressurizing assembly. The additional pressurizing assembly is aimed at applying over-systolic pressure, so as to cause the state of blood flow cessation and enable the occlusion-based measurements. The over-systolic pressure is applied to a location upstream of the measurement location, with respect to a normal blood flow direction.

Preferably, the additional pressurizing assembly is coupled to the clip through a substantially rigid connector engaging the finger along its middle phalanx and proximal intephalangeal joint. This is associated with the fact that occlusion-based measurements are non-volumetric, and the changes in volume of blood in the finger portion undergoing measurement are undesirable for such measurements. However, it is a natural tendency of the finger under pressure (over-systolic pressure) to fold at the proximal intephalangeal joint, thereby causing undesirable changes in blood volume. By providing a substantially rigid support for the finger at the region of the middle phalanx during measurement, such undesirable folding can be avoided.

The present invention also provides an optical measurement device for the non-invasive measurement of patient's blood parameters, the device comprising:

- a finger holder for attaching to the patient's finger, wherein the finger holder is in the form of a clip member, which secures a fingertip between its clamping legs and supports a measuring unit in a manner allowing to apply optical measurements to a measurement location on the finger;
- a first pressurizing assembly operable for applying over-systolic pressure to a location on the patient's finger upstream of said measurement location with respect to a normal blood flow direction, so as to create a state of blood flow cessation at said measurements location;
- a second pressurizing assembly associated with the finger holder and operable for applying desired pressure to the finger in the vicinity of said measurement location; and

- a control system selectively operating the first and second pressurizing assembly, and selectively operating the measuring unit, the control system having a processor that received data indicative of measured signals coming from the measuring unit and analyzes said data.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, a preferred embodiment will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 is a schematic illustration of a probe device according to one embodiment of the invention;

Fig. 2 is a schematic illustration of a probe device according to another embodiment of the invention;

Fig. 3 is a schematic illustration of a probe device according to yet another embodiment of the invention

Figs. 4a to 4d graphically illustrate experimental results obtained with different operational modes of the probe device according to the invention.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

Referring to Fig. 1, there is illustrated a probe device, generally designated **10**, applied to a patient's finger **F** for performing the non-invasive measurement of the patient's blood parameters, such as oxygen saturation, blood pressure or the concentration of various substances, such as hemoglobin, glucose, cholesterol and other analyte concentrations. The probe **10** is in the form of a finger holder **12** mounted on the patient's finger **F**, and is coupled to a control system **14**.

The finger holder **12** is in the form of a clip member **16** having clamping legs – two legs **16A** and **16B** in the present example, pivotal about an axis **17**, for securing the patient's finger **F** therebetween. A pair of manipulating arms **18A** and **18B** operates the pivotal movement of the clamping legs to attach the device to the patient's finger. The clip member **16** carries a measuring unit **20** mounted on its

inner side so as to apply optical measurements to a measurement location L_1 on the patient's finger. Further provided in the probe device **10** is a pressurizing assembly **24** associated with the finger holder **12**. In the present example, the probe device **10** is used for occlusion-based measurements. To this end, an additional pressurizing assembly **22** is provided for applying over-systolic pressure to the blood perfuzed fleshy medium therebelow. When dealing with pulse-oxymetry based measurements, the provision of the pressurizing assembly **22** could be omitted.

The pressurizing assembly (first assembly) **22** is composed of an air cushion cuff **25** in the form of a ring wrapping the patient's finger **F** and a pneumatic drive **26** coupled to the cuff **25** through a pipe **27**. The ring wraps the finger **F** at a location L_2 upstream of the measurement location L_1 with respect to the direction of the normal blood flow. The pressurizing assembly **22**, when actuated, operates to apply over-systolic pressure, e.g., 220-300mmHg (generally, adjustable for each specific patient), at the location L_2, thereby causing the state of blood-flow cessation at the measurement location L_1. The cuff **25** is coupled to the clip member **16** by a substantially rigid connector **28**. The rigid plate-like connector **28** engages the finger along its middle phalanx, preventing its folding at the proximal intephalangeal joint, thereby avoiding undesirable changes in blood volume. The connector **28** is shaped like a plate, and is designed in a manner to enable reciprocating sliding movement of the cuff **25** relative to the clip **16** along the axis of the connector **28**. This enables to adjust the length of the entire finger holder **12** to that of the finger of a specific patient. For example, although not specifically shown, the plate-like connector could be formed with an elongated slot, while the cuff-ring be formed with a projection installed in this slot for reciprocating sliding movement along its axis.

In the present example of Fig. 1, the other (second) pressurizing assembly **24** is composed of a bellow-like air cushion **29** coupled to its pneumatic drive **30** through a pipe **31**. By appropriately expanding or squeezing the cushion **29**, the clamping affect of the legs is adjusted so as to apply a desired pressure onto the patient's finger in the vicinity of the measurement location L_1. It should, however,

be noted that a common pneumatic drive could operate both the cushions **25** and **29**.

As further shown in Fig. 1, a pair of flexible, thermoconductive pads **32** (or pads with built-in heaters), made for example of rubber or silicone, is provided at the inner surfaces of the legs **16A** and **16B**. The pads **32** are coupled to a power source (not shown) operated by a corresponding utility of the control system **14** for applying appropriate, substantially low voltages (e.g., in the range 1V-24V) to the pads **32**, enabling heating the finger portion at the measurement location up to 36-38°. The heating ability of the device increases the accuracy of the non-invasively derived blood-related parameters. The substantially low voltage supply required for heating is, on the one hand, acceptable for medical devices, and, on the other hand, allows for using batteries, thereby rendering the entire device conveniently portable.

The measuring unit **20** does not form part of the present invention, and therefore need not be specifically illustrated and described, except to note that it comprises such main constructional parts as illumination and detection assemblies, generally at **34**, and generates data indicative of the light response of the finger. Generally, the illumination and detection assemblies could be accommodated either at one side of the finger when operating in a reflection mode, or at opposite sides of the finger when operating in a transmission mode. These reflected or transmitted signals present light response of the finger to incident radiation. According to the occlusion-based technique disclosed in the above-indicated PCT application, the measuring unit provides illumination of the finger with at least two different wavelengths, and detects light transmitted therethrough.

Preferably, the illumination unit comprises a plurality of light sources (e.g., LEDs) for illuminating the measurement location with a plurality of different wavelengths in the near infrared spectra. This enables the simultaneous determination of different blood parameters. The wavelengths are selected in accordance with the parameter to be determined. For example, if the hemoglobin concentration is to be determined, the selected wavelengths are in the ranges, where

the absorption properties of the hemoglobin and plasma are more sharply expressed, namely are in the ranges 600-1000nm and 1100-1400nm. If the oxygen saturation is to be determined, the selected wavelengths lie in the range where the difference in the absorption of hemoglobin (Hb) and oxyhemoglobin (HbO_2) are more sharply expressed, namely are in the ranges 600-780nm (where the difference in the sensitivity of HbO_2 and Hb is maximal) and 820-980nm (reference range). When dealing with the glucose concentration, the spectral ranges of 1500-1600nm may be added to the above-mentioned range of 600-1300nm for selecting the operational wavelengths.

The generated data indicative of the detected light (light response of the illuminated medium) is transmitted to the control system **14** for processing and analyzing. To this end, the control system **14** includes a processor **36** operated by suitable software for analyzing the detected signals and determining the desired parameter of the patient's blood, as will be described more specifically further below with reference to Figs. 4a-4d.

Thus, each of the drives **26** and **30** of the first and second pressurizing assemblies **22** and **24**, respectively, whilst being actuated by a corresponding utility of the control system **14**, operates to apply required pressure to the finger portion at locations $\mathbf{L_2}$ and $\mathbf{L_1}$. The pressurizing assembly **24** is first actuated, and when a certain under-systolic pressure is applied to the vicinity of the measurement location $\mathbf{L_1}$, the control system **14** actuates the pressurizing assembly **22** to apply the over-systolic pressure to the location $\mathbf{L_2}$. When the blood flow cessation state is created, the control system **14** operates the measurement unit **20** to illuminate the measurement location with different wavelengths and detect the light response. The application of over-systolic pressure (location $\mathbf{L_2}$) is maintained for a period of time, so as not to cause irreversible changes in the finger, and then, the control system operates the drive **26** to release this pressure. The pressurizing assembly **24** applies a different value of the under-systolic pressure, the pressurizing assembly **22** is operated to perform a further occlusion-release session. During each such occlusion-release session, the light response of the measurement location as a

function of time is determined. The effective measurements, i.e., the results that have to be analyzed, are those taken at the state of blood flow cessation.

The operational mode of the device **10** may be such that the control system **14** actuates the measuring unit **20** for performing continuous measurements starting prior to the application of over-systolic pressure. In this case, only those signals, which are associated with the state of blood cessation, are taken into consideration. Measurements taken during the time period prior to the establishment of this state should be disregarded, due to the unavoidable influence of motional and/or other artifacts causing non-monotonic fluctuations of the light transmission. According to an alternative operational mode of the device **10**, the control system **14** actuates the measuring unit **20** a small period of time after the application of the over-systolic pressure. During the time period corresponding to the existence of the state of blood cessation, relative light transmission of blood is observed, which reaches its maximum and may last generally from one second to several minutes.

To obtain meaningful results, either at least two timely separated measurement sessions should be considered, at least one of them being that taken during the state of blood cessation, or a single long continuous measurement session should be considered starting after the establishment of the state of blood cessation. During the first measurement session, the control system **14** operates to maintain the cuff **25** and the cushion **29** in their squeezed position, and operates the heating element **32** to heat the finger in the vicinity of the measurement location. The control system **14** then operates the pneumatic drives **26** and **30** to release the pressure. The squeezing action of the cuff **25** is ceased, and after a short delay preset by the respective software in the control unit, the blood flow sharply increases until it reaches new steady state. Then, the control system **14** actuates the second measurement session at a state of the transitional blood flow. The illumination assembly continues to illuminate the finger, but squeezing is halted. The detection assembly, being synchronized by the control system **14**, detects the light response of the finger. In other words, the control system **14** selectively

operates the measuring unit **20** and the pressurizing assemblies **22** and **24**, and analyzes data coming from the measuring unit, as will be described further below.

Reference is made to Fig. 2, illustrating a probe device **100** according to another embodiment of the invention. To facilitate understanding, the same reference numbers are used for identifying those components which are common in the devices **10** and **100**. The device **100** is constructed generally similar to the device **10**, but has a somewhat different design of a finger holder **112**. Here, a pressurizing assembly **124** utilizes a cuff-like cushion **129** coupled to a pneumatic drive **30** through a pipe **31**. In other words, the second pressurizing assembly **124** is constructed generally similar to the first assembly **22**, but is associated with the measurement location L_1 for applying under-systolic pressures thereto. The heating element **32** may be attached to the surface of the cushion **129** contacting the finger skin. The operation of the device **100** is similar to that of the device **10**. It should, however, be noted, that the pressurizing assembly **124** can be used in combination with the assembly 24 (Fig. 1), rather than replacing it.

Fig. 3 illustrates a probe device **200** having a somewhat different design as compared to the previously described examples. Here, a pressurizing assembly **224**, that applies under-systolic pressures to the measurement location L_1, includes a balloon-like flat cushion **229**, which is accommodated either between the flexible pad **32** and the inner surface of the clamping leg **16B**, or inside the pad 32, and is coupled to the drive **30** through the pipe **31**. To prevent the opening of the clip member, when in the expanded position of the cushion **229**, a lock mechanism **230** is appropriately provided.

It should be noted, although not specifically shown, that the clip member may have a four-legged design, in which case one pair of legs engages the finger at its top and bottom thereof, and the other pair of legs engages the opposite sides of the finger. Such four-sided support of the fingertip prevents its folding at the distal phalanx, thereby avoiding undesirable blood volume changes.

It should also be noted that the rigid connector **28** may be located at either side of the patient's finger. Alternatively, a pair of such connectors can be used

located at opposite sides of the finger. Additionally, the processor may be accommodated within the cuff **25**, and wires, if any, connecting the processor to the output circuit of the measuring unit **20**, may pass through the rigid connector.

Turning now to Figs. 4a-4d, the advantageous features of the present invention are graphically illustrated. Figs. 4a and 4b illustrate, respectively, graphs G_1 and G_2 presenting experimental results obtained with two different modes of the probe device **10**, namely, when the pressurizing assembly **24** is in its active (operational) and passive (non-operational) modes. Each of the graphs G_1 and G_2 corresponds to the concentration of hemoglobin derived from measurement data obtained with the measurement unit **20** as the function of the hemoglobin concentration obtained with one of the conventional techniques (invasive). To plot each of the graphs, ten measurement points were used. The results show that with the active mode of the pressurizing assembly, when a desired, optimal under-systolic pressure is applied to the measurement location, the measured correlation between the concentration values obtained with different techniques is about 0.91, and the standard deviation is 0.9. While with the passive mode of the pressurizing assembly, these parameters are, respectively, 0.79 and 1.3.

Figs. 4c and 4d illustrate examples of the technique of the present invention enabling the determination of the desired, optimal pressure to be applied by the pressurizing assembly **24** to a specific patient. Fig. 4c illustrates four graphs H_1, H_2, H_3 and H_4. Graphs H_1 and H_2 correspond to the parametric slopes as functions of the pressure applied by the assembly **24**, wherein the parametric slopes were obtained for two different pairs of wavelengths: (1) λ_1=660 and λ_2=940nm, and (2) λ_1=1300 and λ_2=940nm, respectively.

The slope-based technique of determining the blood substance concentration is disclosed in the above-indicated PCT application assigned to the assignee of the present application. A parametric slope is determined as the transmission logarithm at the wavelength λ_2, i.e., Log(λ_2), versus the transmission logarithm at the wavelength λ_1, i.e., Log(λ_1), over a certain time interval (e.g., long occlusion) or at timely separated occlusion stages (i.e., multiple occlusion-release sessions). It

should be understood that the slope-based technique may be applied with the pulse-oxymetry as well. In this case such a slope correspond to AC/DC ratio that enables the determination of blood-related parameters. In other words, the parametric slope is a linear function of Log(λ_2) versus Log(λ_1), whose slope can be determined, for example, by a known linear regression algorithm.

Graphs **H_3** and **H_4** correspond to the slope-error (i.e., standard deviation) as the function of pressure, for the above parametric slopes, respectively. To determine the slope-error, several measurement sessions were taken with the same pairs of wavelengths, corresponding parametric slopes were calculated, and standard deviation values were determined. As clearly seen in the figure, the maximum value (0.55) of the slope in graph **H_1**, which represents certain results criteria for the determination of the oxygen saturation, corresponds to the minimum value (0.04) of the respective slope-error in graph **H_3** at the pressure value of about 100mmHg. Similarly, the minimum value (0.35) of the slope in graph **H_2**, which represents another results criteria, corresponds to the minimum value (0.04) of the respective slope-error in graph **H_4** at the pressure value of about 100mmHg. Thus, this pressure is the optimal pressure for this specific patient, and should be applied to the vicinity of the measurement location on his finger during the optical measurements

Fig. 4d illustrates the amplitude of the measured signal as the function of the applied pressure. As shown, at a certain pressure value (about 120mmHg), the amplitude reaches its maximal value.

Hence, the experimental results show that optical parameters of the patient's blood, such as slope and amplitude of the light response, changes with the pressure variations. This enables to select the optimal pressure value (or range) to increase the accuracy of measurements, and obtain better results. Generally speaking, the determination of the optimal pressure value is based on a certain optical criteria, such as minimum of the standard deviation, maximum amplitude of the measured optical signal, AC/DC ratio, parametric slope, etc. It should be understood that the pressure values in the above examples are relevant only for the specific design of

the probe used in the experiments, and may be different for different patients and different probe configurations. As indicated above, the rigidity of the constructional elements of the probe also affects the optimal pressure value to be used for optimizing the measurement results.

Those skilled in the art will readily appreciate that various modifications and changes can be applied to the preferred embodiments of the invention as hereinbefore exemplified without departing from its scope defined in and by the appended claims.

CLAIMS:

1. A method of non-invasive optical measurement of at least one parameter of the patient's blood, the method comprising the steps of:

(a) applying a probe device to the patient's blood perfused fleshy medium, wherein the probe device carries an optical measurement unit and a pressurizing assembly operable to apply controllably varying substantially under-systolic pressure to a measurement location on said medium;

(b) performing several measurement sessions to a measurement location on said medium to detect light response of the medium and generate measured data indicative thereof, and simultaneously varying the pressure applied to the vicinity of said measurement location, wherein each measurement session utilizes at least two different wavelength of incident light;

(c) analyzing the light response of the medium corresponding to different wavelengths of the incident light and different pressure values, and determining an optimal pressure value, so as to utilize the corresponding light response of the medium for deriving therefrom said at least one blood parameter.

2. The method according to Claim 1, wherein said optimal pressure value is determined as the pressure value corresponding to certain optical criteria results.

3. The method according to Claim 2, wherein the criteria results utilize at least one of the following parameters: minimum of standard deviation, maximum of the amplitude of the light response, AC/DC ratio, parametric slope.

4. A probe device to be used in non-invasive optical measurements of a patient's blood parameter, the probe device comprising a finger holder having a clip member that secures a fingertip between its clamping legs, wherein the finger holder supports a measuring unit for applying optical measurements to a measurement location on the finger, and carries a pressurizing assembly operable

for applying controllably variable, substantially under-systolic pressure to the finger in the vicinity of said measurement location.

5. The probe according to Claim 4, further comprising an additional pressurizing assembly operable for applying over-systolic pressure to a location on the patient's finger upstream of said measurement location with respect to a normal blood flow direction, so as to create a state of blood flow cessation at said measurement location.

6. The probe according to Claim 4, wherein said pressurizing assembly is associated with manipulating arms of the clip member, such as to controllably vary pressure of the clamping legs onto the fingertip secured therebetween.

7. The probe according to Claim 4, wherein said pressurizing assembly comprises a bellow-like air cushion, which is interconnected by its opposite ends between the manipulating arms, and is coupled to a pneumatic drive selectively operable to supply controllably variable pressure.

8. The probe according to Claim 4, wherein said pressurizing assembly is associated with the measurement location, and accommodated on the inner side of the clip member.

9. The probe according to Claim 8, wherein said second pressurizing assembly comprises a cuff-like cushion coupled to a pneumatic drive selectively operable to supply the controllably variable pressure.

10. The probe according to Claim 4, wherein said pressurizing assembly comprises a substantially flat balloon-like cushion coupled to a pneumatic drive, the balloon-like flat cushion being accommodated between the inner surface of the upper clamping leg and a substantially flexible pad contacting the patient's finger.

11. The probe according to Claim 4, wherein said additional pressurizing assembly comprises an air cushion cuff-ring wrapping said location upstream of the measurement location, and a pneumatic drive coupled to the cuff-ring so as to apply said over-systolic pressure to the upstream location.

12. The probe according to Claim 11, further comprising a substantially rigid connector between the clip member and an element of the additional pressurizing

assembly located at said upstream location on the finger, the connector being adapted to engage the finger along its middle phalanx and proximal intephalangeal joint, thereby preventing it from folding during the measurements.

13. The probe according to Claim 12, wherein said connector allows for reciprocating movement of said element of the additional pressurizing assembly along the finger with respect to the clip member.

14. The probe according to Claim 4, wherein said clip member is provided at the inner surface thereof with a flexible member for wrapping the measurement location of the finger, said flexible member being made of a thermoconductive material for heating said measurement location up to desired temperature.

15. The probe according to Claim 5, wherein said measuring unit, and the pressurizing assemblies are operated by a control system, having a processor for receiving and analyzing data coming from the measuring unit and indicative of the measured light response of the finger.

16. A pulse-oxymeter for non-invasive measurements of blood-related parameters of a patient, the pulse-oxymeter comprising the probe device of Claim 4 and a control system that operates the pressurizing assembly and the measurement unit and generates data indicative of the measured parameters.

17. An optical measurement device for the non-invasive measurement of patient's blood parameters, the device comprising:

- a finger holder for attaching to the patient's finger, wherein the finger holder is in the form of a clip member, which secures a fingertip between its clamping legs and supports a measuring unit in a manner allowing to apply optical measurements to a measurement location on the finger;
- a first pressurizing assembly operable for applying over-systolic pressure to a location on the patient's finger upstream of said measurement location with respect to a normal blood flow direction, so as to create a state of blood flow cessation at said measurements location;

- a second pressurizing assembly associated with the finger holder and operable for applying desired pressure to the finger in the vicinity of said measurement location; and
- a control system selectively operating the first and second pressurizing assembly, and selectively operating the measuring unit, the control system having a processor that received data indicative of measured signals coming from the measuring unit and analyzes said data.

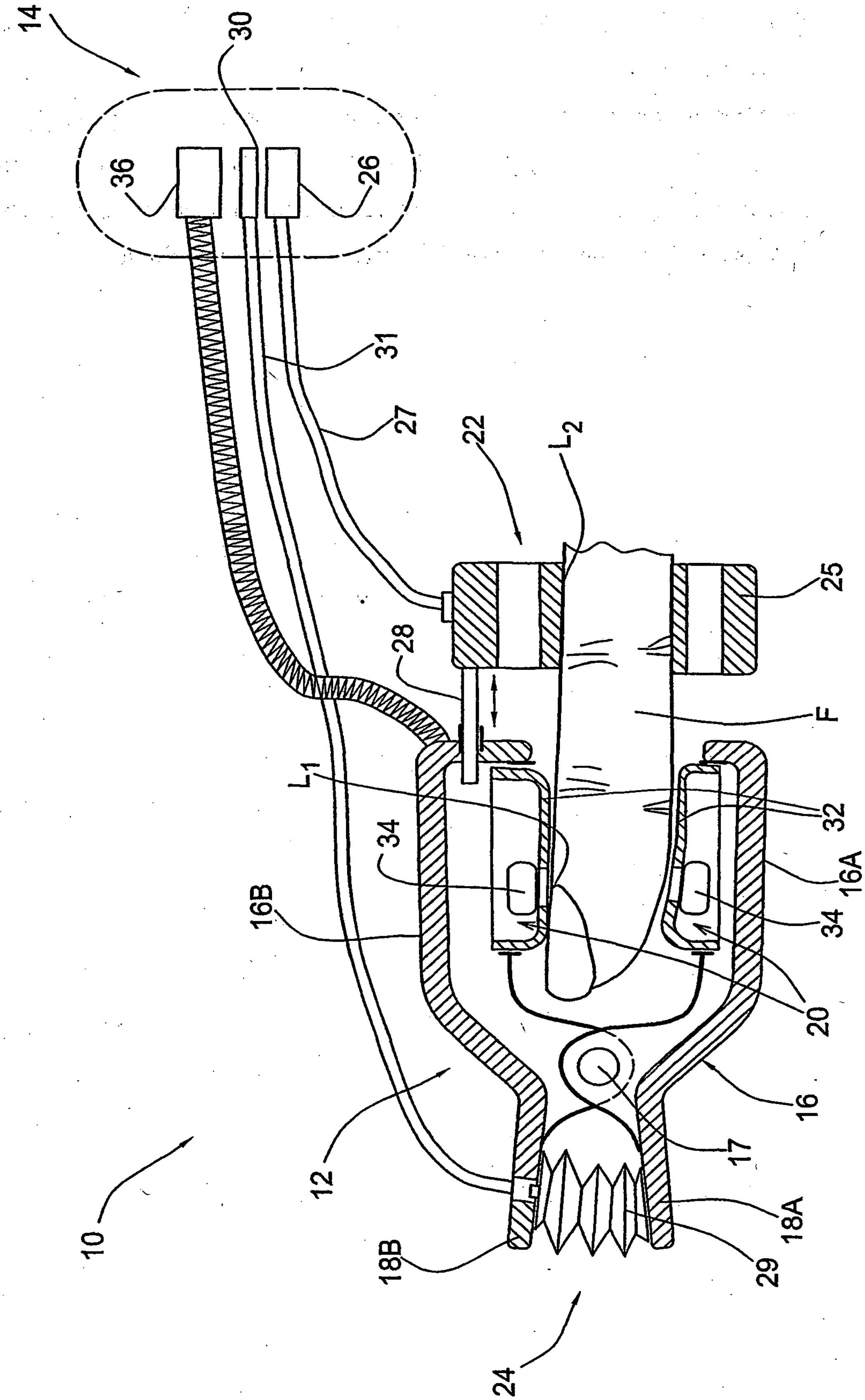

14
30
36
26
31
27
22
L2
25
28
F
L1
32
34
16A
16B
34
20
16
12
17
10
18A
18B
29
24

FIG. 1

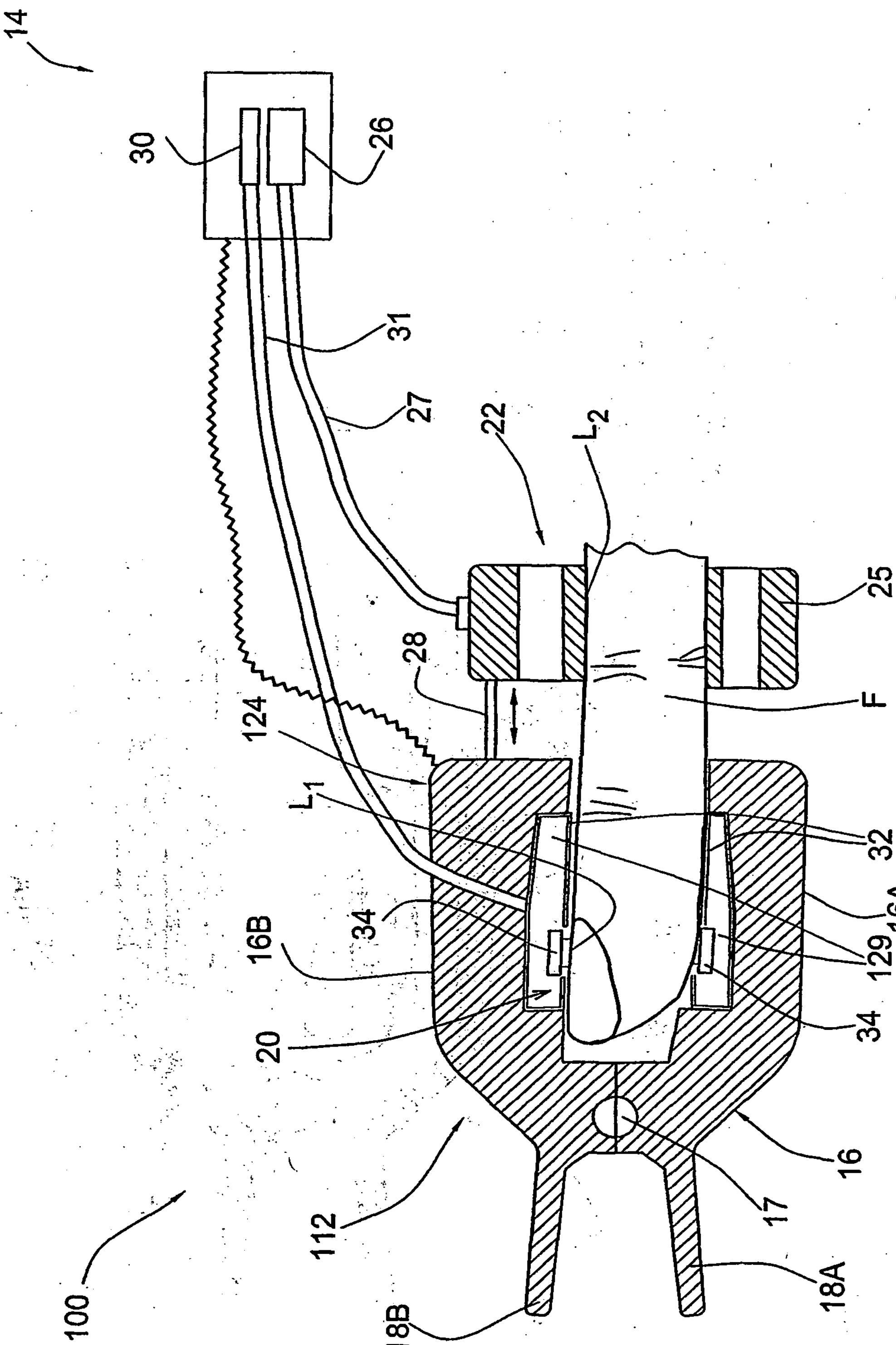

14
30
26
31
27
22
L2
25
28
F
124
L1
32
16A
129
34
16B
34
20
16
17
112
100
18A
18B

FIG. 2

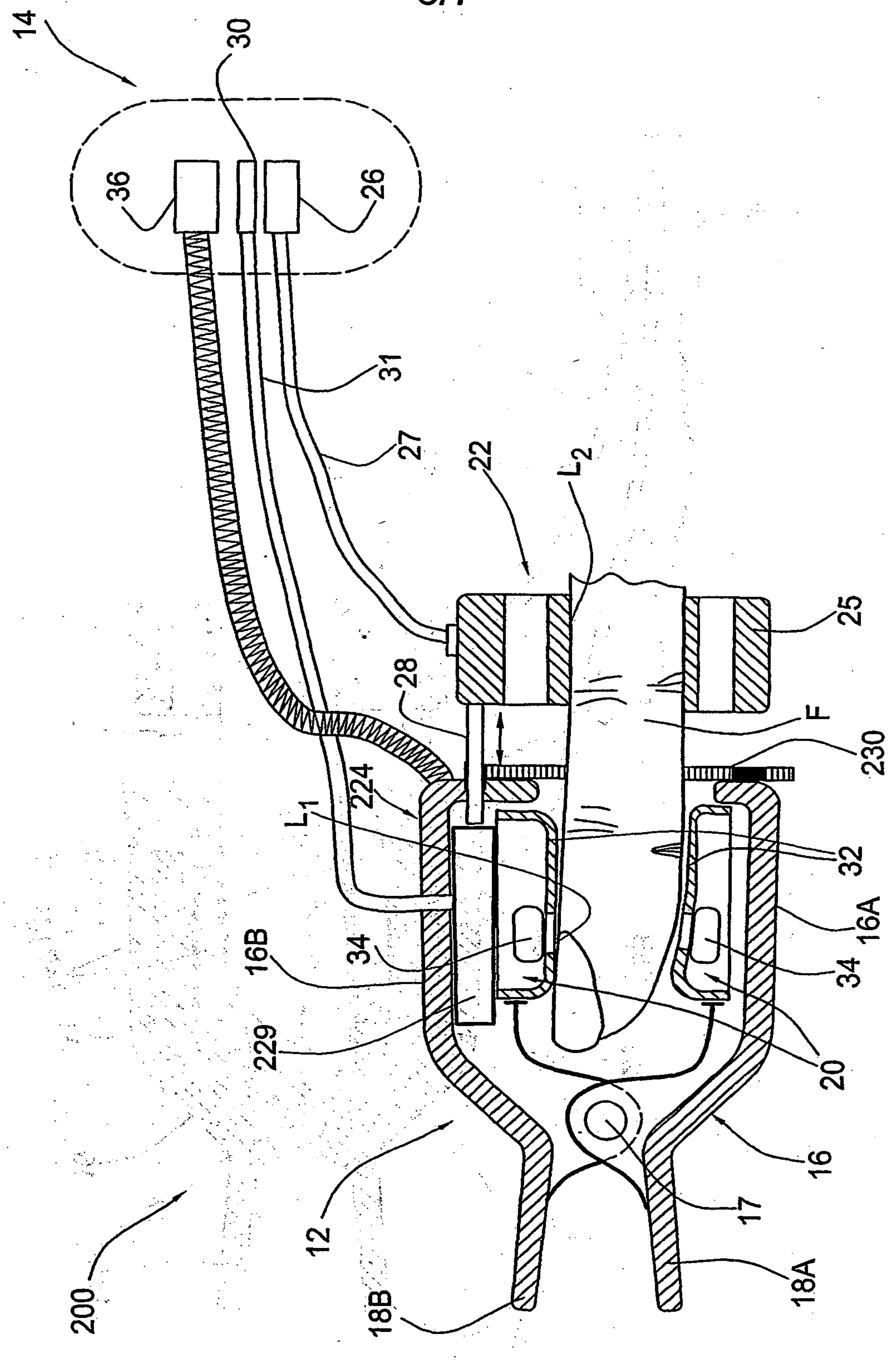

14
30
36
26
31
27
22
L_2
25
28
F
230
224
L_1
32
16A
34
16B
34
229
20
16
12
17
200
18A
18B

FIG. 3

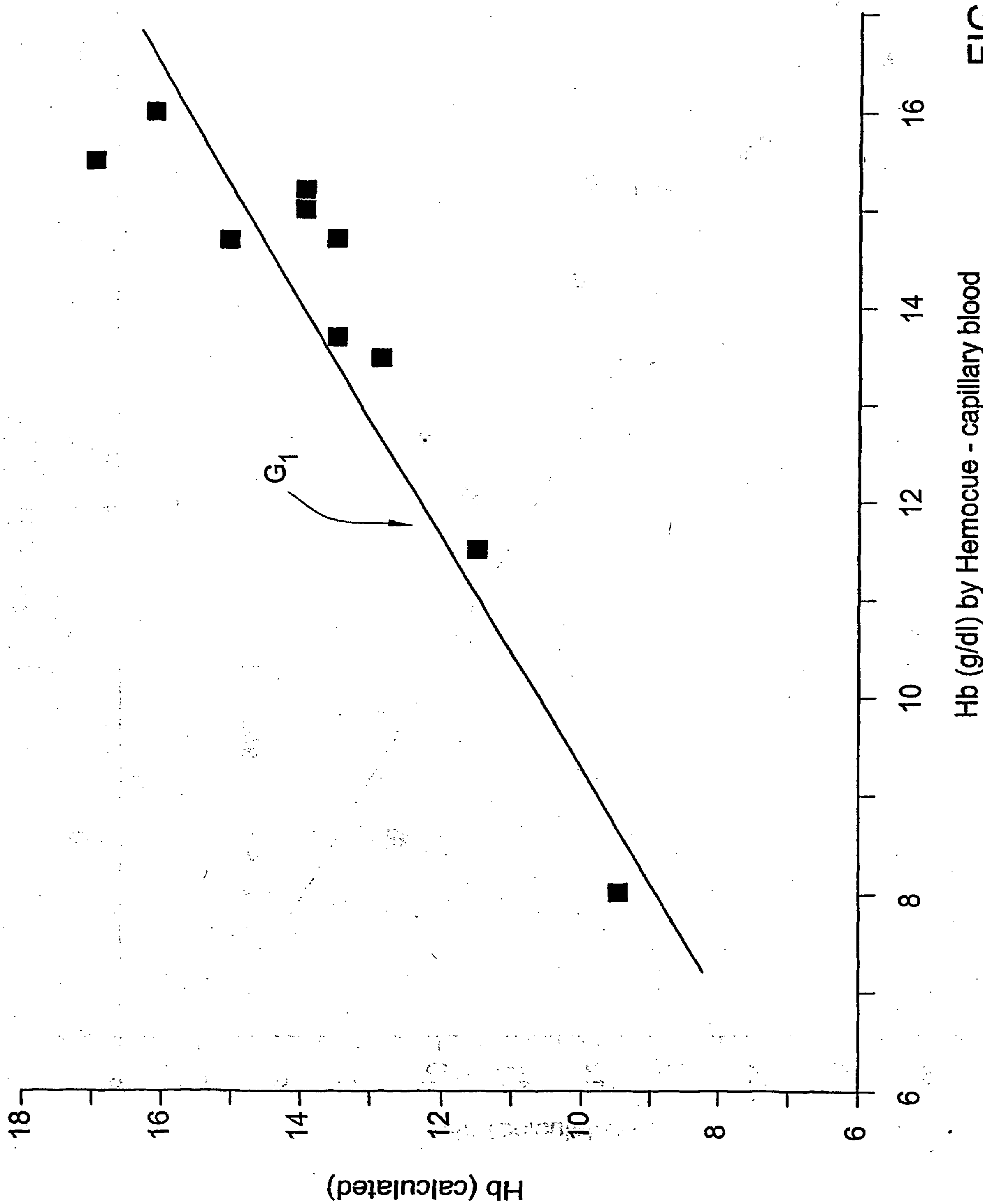
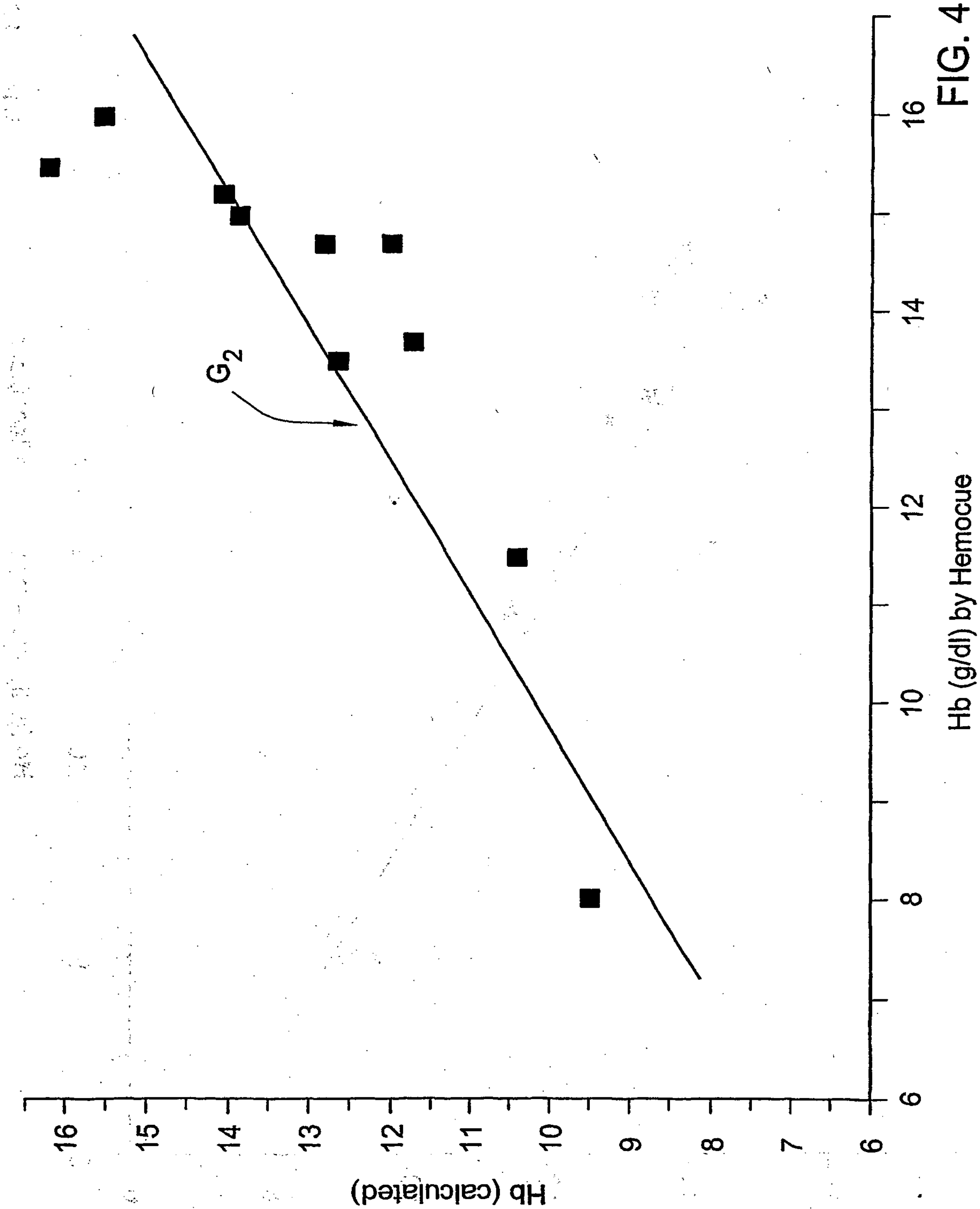
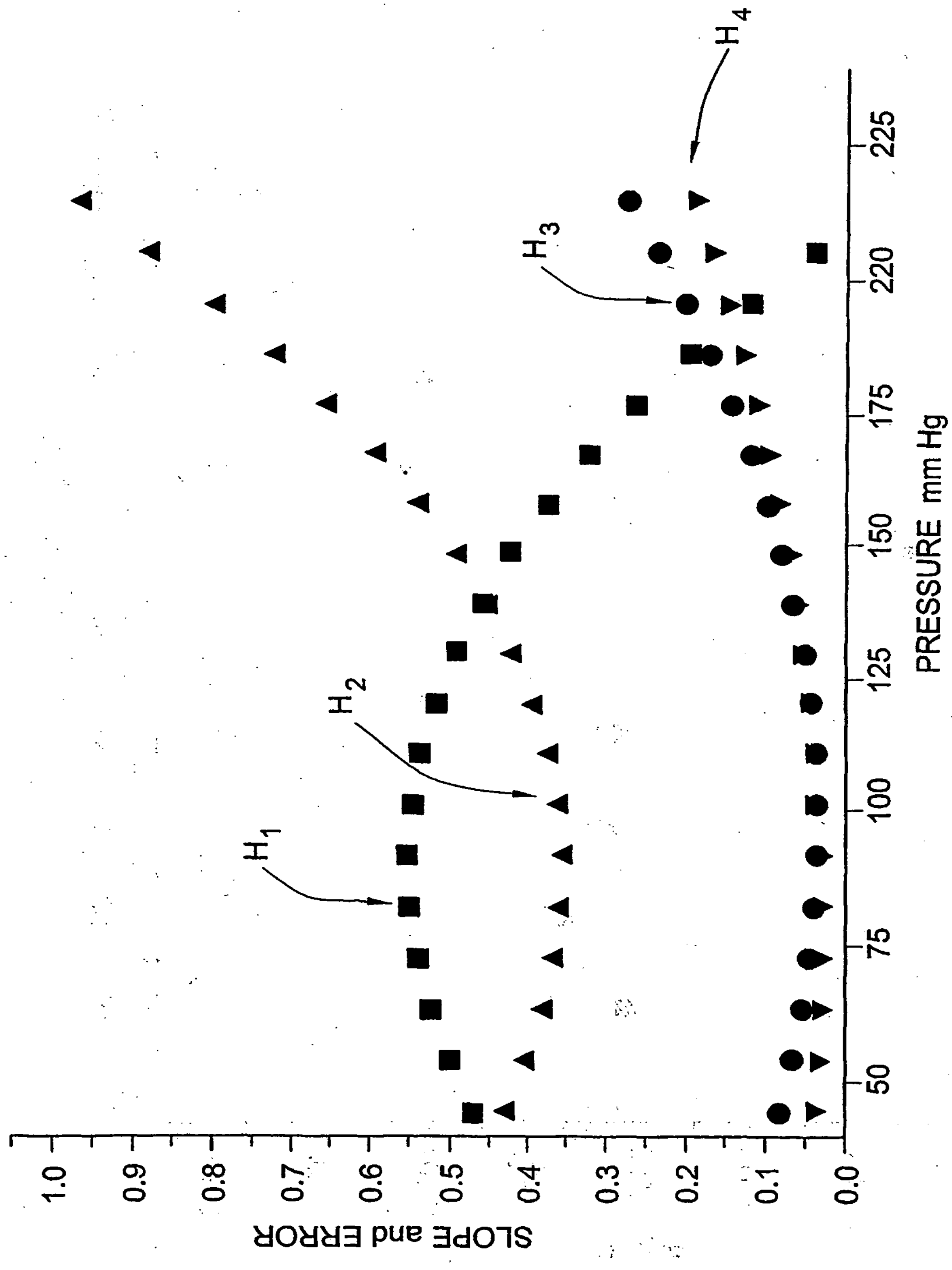

Hb (calculated)
18
16
14
12
10
8
6
Hb (g/dl) by Hemocue - capillary blood
6
8
10
12
14
16
G_1

FIG. 4A



G2
Hb (calculated)
Hb (g/dl) by Hemocue
6
7
8
9
10
11
12
13
14
15
16
6
8
10
12
14
16

FIG. 4B



SLOPE and ERROR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
50
75
100
125
150
175
200
225
PRESSURE mm Hg
H_1
H_2
H_3
H_4

FIG. 4C

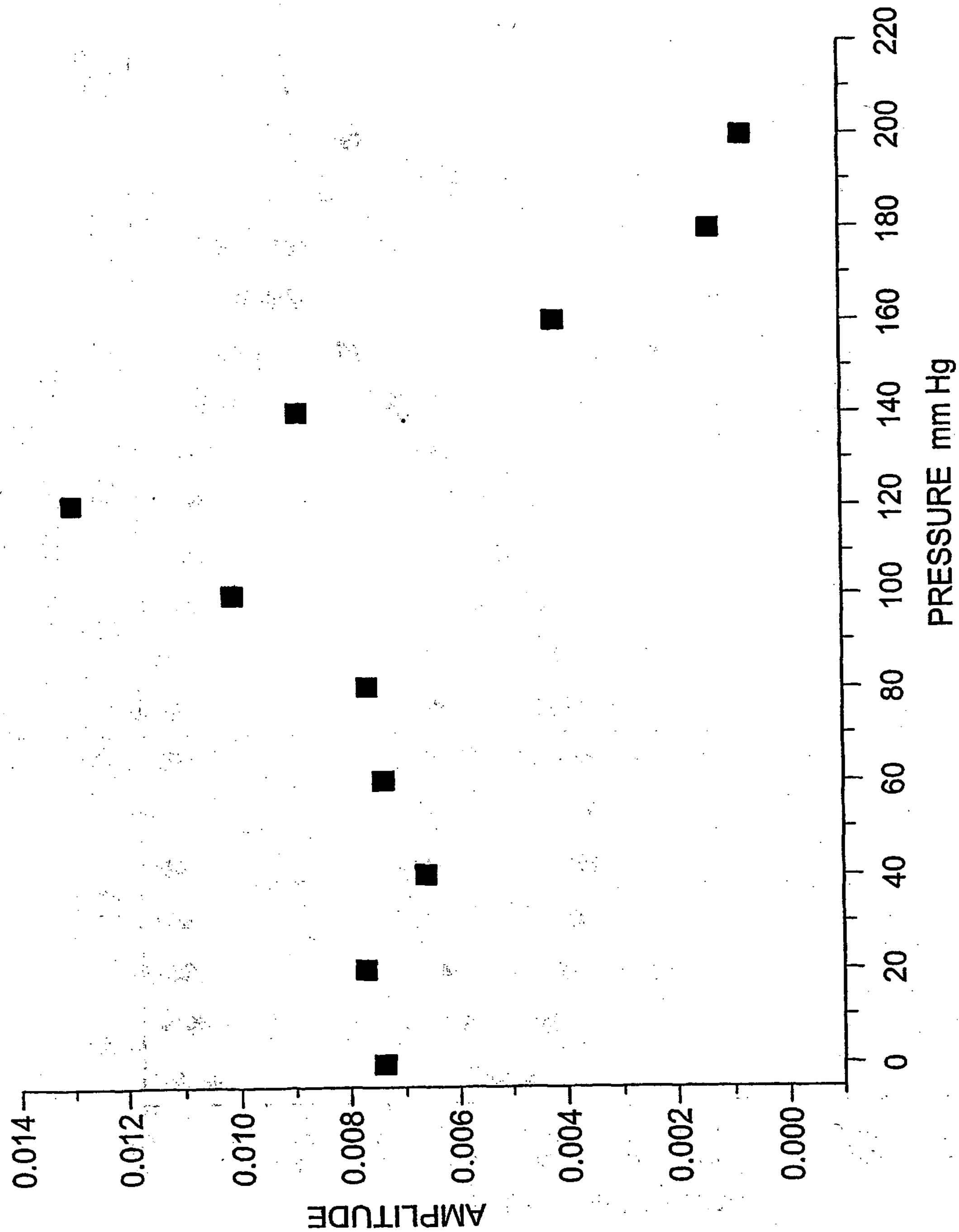

AMPLITUDE
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0
20
40
60
80
100
120
140
160
180
200
220
PRESSURE mm Hg

FIG. 4D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 01/00250

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 827 181 A (DIAS J FLEMING ET AL) 27 October 1998 (1998-10-27) column 2, line 45 -column 3, line 44 column 4, line 40 -column 5, line 26; tables 1,3	1
A	US 5 111 817 A (WALLACE WILLIAM D ET AL) 12 May 1992 (1992-05-12) column 4, line 64 -column 6, line 27 column 11, line 40 -column 12, line 37; tables 1,2	1
A	EP 0 227 119 A (NIPPON COLIN CO LTD) 1 July 1987 (1987-07-01) column 11, line 15 -column 14, line 5; table 2	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 August 2001	09/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weihs, J

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92 21281 A (SUSI ROGER E) 10 December 1992 (1992-12-10) page 11, line 20 -page 13, line 14; table 2	4
A	WO 99 65384 A (FINE ILYA ;ORSENSE LTD (IL)) 23 December 1999 (1999-12-23) cited in the application page 4, line 23 -page 9, line 25; tables 1-3	1,5,17

INTERN/ ONAL SEARCH REPORT

Information on patent family members

...al Application No
PCT/IL 01/00250

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
US 5827181	A	27-10-1998	US	6113541	A	05-09-2000
US 5111817	A	12-05-1992	US	5423322	A	13-06-1995
EP 0227119	A	01-07-1987	JP	62155829	A	10-07-1987
			DE	3685314	D	17-06-1992
			US	4780824	A	25-10-1988
WO 9221281	A	10-12-1992	EP	0587718	A	23-03-1994
WO 9965384	A	23-12-1999	AU	4643599	A	05-01-2000
			EP	1087693	A	04-04-2001

PATENT COOPERATION TREATY (1)

RECEIVED
SEP 2 6 2003
BROMBERG & SUNSTEIN

From the INTERNATIONAL SEARCHING AUTHORITY

To: BROMBERG & SUNSTEIN LLP Attn. Petuchowski, Samuel J. 125 Summer Street Boston, Massachusetts 02110-1618 UNITED STATES OF AMERICA

DOCKETED

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 18/09/2003
Applicant's or agent's file reference 1118/185 WO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 03/ 17024	International filing date *(day/month/year)* 30/05/2003
Applicant MASSACHUSETTS INSTITUTE OF TECHNOLOGY	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO
   34, chemin des Colombettes
   1211 Geneva 20, Switzerland
   Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

   Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

   Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chantal Ullrich

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1118/185 WO	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 03/ 17024	International filing date *(day/month/year)* 30/05/2003	(Earliest) Priority Date *(day/month/year)* 11/06/2002
Applicant MASSACHUSETTS INSTITUTE OF TECHNOLOGY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
      [ ] contained in the international application in written form.
      [ ] filed together with the international application in computer readable form.
      [ ] furnished subsequently to this Authority in written form.
      [ ] furnished subsequently to this Authority in computer readble form.
      [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
      [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).
3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1
   [X] as suggested by the applicant.
   [ ] because the applicant failed to suggest a figure.
   [ ] because this figure better characterizes the invention.
   [ ] None of the figures.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]: "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]: "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/17024

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00 A61B5/024

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 07172 A (SIEMENS AG) 19 February 1998 (1998-02-19) page 4, line 1 -page 9, line 16; claims 1,3,15,22; figure 1	1-5,7-11
X	WO 01 67946 A (FINAROV ALEXANDER ;FINE ILYA (IL); ORSENSE LTD (IL)) 20 September 2001 (2001-09-20) page 1, column 2, line 21 -page 3, column 1, line 25; claims 1,5,17; figure 1	1-6
X	US 5 964 701 A (SIU KAI-YEUNG SUNNY ET AL) 12 October 1999 (1999-10-12) the whole document	1-5,7-11
X	WO 00 64338 A (MASSACHUSETTS INST TECHNOLOGY) 2 November 2000 (2000-11-02) the whole document	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 September 2003	18/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chopinaud, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/17024

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9807172	A	19-02-1998	AT	191100	T	15-04-2000
			CZ	9900377	A3	12-05-1999
			DE	29718230	U1	12-02-1998
			DE	59701331	D1	27-04-2000
			WO	9807172	A1	19-02-1998
			EP	0917723	A1	26-05-1999
			ES	2145628	T3	01-07-2000
			HU	0001844	A2	28-09-2000
			PL	331379	A1	05-07-1999
			SI	917723	T1	31-10-2000
WO 0167946	A	20-09-2001	AU	3953201	A	24-09-2001
			CN	1418072	T	14-05-2003
			EP	1263315	A1	11-12-2002
			WO	0167946	A1	20-09-2001
			US	2002173709	A1	21-11-2002
US 5964701	A	12-10-1999	EP	0934021	A2	11-08-1999
			JP	2001504718	T	10-04-2001
			KR	2000052757	A	25-08-2000
			WO	9817172	A2	30-04-1998
WO 0064338	A	02-11-2000	WO	0064338	A2	02-11-2000
			US	6402690	B1	11-06-2002